



Hereditary Angioedema Treatments Therapeutic Class Review (TCR)

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Columbia, Maryland 21046

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
ecallantide (Kalbitor®) ¹	Dyax	Treatment of acute HAE attacks in ages ≥ 12 years
icatibant (Firazyr®) ²	Shire	Treatment of acute HAE attacks in ages ≥ 18 years
C1-esterase inhibitor [human] (Berinert®) ³	CSL Behring	Treatment of acute HAE facial, laryngeal, or abdominal attacks in adult and pediatric patients Safety and efficacy for prophylactic therapy have not been established
C1-esterase inhibitor [Human] (Haegarda®) ⁴	CSL Behring	Routine prophylaxis to prevent HAE attacks in adolescent and adult patients
pdC1-INH [Human] (Cinryze®) ⁵	Shire	Routine prophylaxis against angioedema attacks in adolescents and adult with HAE
rhC1-INH [recombinant] (Ruconest®) ⁶	Salix	Treatment of acute attacks in adult and adolescent patients with HAE Limitation of use: effectiveness has not been established in HAE patients with laryngeal attacks

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema

OVERVIEW

Hereditary angioedema (HAE) is a rare dominant, autosomal genetic disorder that affects between 6,000 and 30,000 individuals in the United States (U.S.).⁷ Patients with HAE have low levels of endogenous or functional C1 esterase inhibitor (C1-INH). HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous (SC) or submucosal edema involving the skin or mucosal tissues of the upper respiratory and gastrointestinal (GI) tracts. Although swelling can resolve spontaneously in several days, without treatment, laryngeal edema may be fatal and the pain of GI attacks can be incapacitating. Symptoms can begin as early as 2 years of age and persist throughout life with unpredictable severity and frequency of attacks. It is thought that minor trauma and stress can lead to an attack; however, many attacks can occur without any apparent trigger.

There are 2 types of C1-INH deficient HAE. The most common type (Type I), in which the body does not produce enough C1-INH, occurs in about 85% of patients with the condition.⁸ Type II HAE is characterized by the presence of normal or high levels of a dysfunctional C1-INH.

The complications of HAE do not respond well to the usual therapies for mast-cell mediated angioedema, including antihistamines, epinephrine, and glucocorticosteroids, necessitating the establishment of an accurate diagnosis.⁹ Plasma complement protein 4 (C4) antigenic levels should be measured in any patients suspected of having HAE. C1-Inhibitor antigenic and functional levels should be tested to confirm the HAE diagnosis if the C4 level is decreased and in cases where C4 level is normal and most or all of the clinical criteria listed above are met.

HAE prophylaxis is needed to reduce potential edema caused by a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (long-term prophylaxis). The 2013 U.S. Hereditary Angioedema Association (HAEA) consensus document recommends short-term prophylaxis prior to medical, dental, or surgical procedures.¹⁰ The

need for long-term prophylaxis should be made based on attack frequency, attack severity, comorbid conditions, access to treatment, and patient experience and preference. Because disease severity may change over time, the need for continued long-term prophylaxis should be assessed periodically. In addition, patients on prophylactic therapy should also have access to on-demand treatment for acute attacks.

In 2016, the U.S. HAEA Medical Advisory Board and leaders of the HAE Patient's Association, developed consensus recommendations to help with recognition, diagnosis, treatment of attacks, and prophylaxis of children with HAE.¹¹ These recommendations state that an accurate diagnosis of HAE must be established prior to discussing treatment options. An accurate diagnosis may be accomplished by measurement of C4 and assessment of C1-INH activity (functional and quantitative). Additionally, treatment strategies should be individualized based primarily on patient specific factors such as age, comorbidities, and access to emergency medical facilities. The goal of treatment in children with HAE is to prevent mortality, minimize morbidity, and to allow for a normal childhood. The consensus recommendation recognize that pdC1-INH (Berinert) is currently the only agent FDA-approved to treat all pediatric ages. Thus, pdC1-INH (Berinert) 20 U/kg is the preferred treatment of choice for short-term prophylaxis prior to medical, surgical or dental procedures. The consensus recommendations also indicate pdC1-INH (Berinert) is appropriate for long-term prophylaxis in the pediatric population. However, it should be noted that the safety and efficacy of prophylactic therapy with this agent has not been established. In June 2017, a subcutaneous C1-esterase inhibitor (Haegarda) formulation, was approved for routine prophylaxis prevention of HAE attacks in adolescent and adult patients; it was not available at the time of guideline publication.¹²

An international consensus group, which included representation from the U.S., recommended the use of plasma-derived human C1-INH (Berinert, Cinryze) for acute treatment, short-term prophylaxis, and long-term prophylaxis in pregnant patients and stated this should also be available during labor and delivery, if needed.¹³ Tranexamic acid or fresh frozen plasma (FFP) may be used for long-term prophylaxis if plasma-derived human C1-INH is unavailable. Data in this population using recombinant C1-INH (Ruconest) were not available at the time of this publication. Traditionally, 17-alpha-alkylated androgens (e.g., danazol) have been used for HAE prophylaxis. This oral anabolic androgen is associated with many adverse effects and is contraindicated in pediatrics and pregnancy/lactation. The HAEA evidence-based recommendations advises against the use of anabolic androgens for long-term prophylaxis for patients who are intolerant to anabolic androgen or if the effective dose exceeds the equivalent of 200 mg danazol per day.¹⁴ Also, failure of androgen therapy should not be a prerequisite to prophylactic C1-INH therapy. Antifibrinolytic agents (e.g., tranexamic acid and aminocaproic acid) have also been used to prevent HAE attacks, but have limited efficacy and significant toxicity. C1-INH (Cinryze) has demonstrated effectiveness in short- and long-term prophylaxis. Haegarda was not available at the time of this guidelines development.

In 2017, a international consensus group provided guidance on the diagnosis and management of pediatric patients with C1-INH-HAE.¹⁵ Symptoms of C1-INH-HAE often are first seen in childhood and the differential diagnosis can be difficult to determine since abdominal pain is common in the general pediatric population. A more severe course of the disease may be foreseen by the early onset of symptoms. All neonates/infants with an affected C1-INH-HAE family member should be screened for C1-INH deficiency. Confirmation of the diagnosis should be made after 1 year of age since C1-INH levels may be lower before this time than in adults. Patients care should be followed at an HAE comprehensive care center. Therapeutic prophylaxis includes either short-term prophylaxis before a

precipitating event or long-term prophylaxis. As in adults, indications for short-term prophylaxis in pediatrics include patient-specific triggers, medical and dental procedures. For most minor interventions, the group recommends on-demand treatment if a swelling event occurs instead of prophylaxis treatment (Level III evidence). For interventions requiring airway manipulation or that may precipitate tissue swelling, prophylaxis with a dose of 15 to 30 units per kg pdC1-INH (Berinert) is recommended (Level III evidence). In the event approved short-term prophylaxis HAE treatment is not available with a planned procedure, oral attenuated androgens (e.g., danazol) or antifibrinolytics (e.g., tranexamic acid) may be considered, starting at least 5 days before and continued for 2 days after the procedure (Level III evidence); approved on-demand treatment should be made available in case of failure. Long-term prophylaxis is controversial in adults and pediatrics, and may be considered to maximize quality of life. Agents to consider include antifibrinolytics (tranexamic acid is agent of choice in select patients), attenuated androgens, and pdC1-INH. The consensus group state that pdC1-INH may be the safest option for long-term prophylaxis, and are recommended over attenuated androgens. For acute treatment, they give no preference to one drug or another that are approved for pediatric use. Haegarda, was not available at the time of this guideline development.

The 2012 Hereditary Angioedema International Working Group (HAWK) evidence-based recommendations and 2012 World Allergy Organization evidence-based recommendations consider C1-INH (Berinert, Cinryze, Ruconest), ecallantide (Kalbitor), or icatibant (Firazyr) all first-line agents in HAE treatment and support patient access to at least 1 of these medications.^{16,17} No 1 agent is recommended over another. Fresh frozen plasma (FFP) has been used in the absence of these agents with some success. Antihistamines, corticosteroids, or epinephrine have little or no clinical benefit for treatment of HAE. Haegarda, was not available at the time of this guideline development. In 2013, a joint task force representing members of the American Academy of Allergy, Asthma, and Immunology (AAAAI); the American College of Allergy, Asthma, and Immunology (ACAAI); and the Joint Council of Allergy, Asthma, and Immunology (JCAAI) also agreed with the above recommendations.¹⁸ A 2014 consensus report from the HAWK group on various types of angioedema also confirmed the above recommendations for treatment of HAE.¹⁹

PHARMACOLOGY^{20,21,22,23,24,25}

HAE is caused by mutations in the C1-INH located on chromosome 11q and is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of high molecular weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is not present; thus, during HAE attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms, including localized swelling, inflammation, and pain.

Berinert, Cinryze, and Haegarda are human plasma-derived, purified, pasteurized, lyophilized concentrate of C1-INH. Ruconest is a recombinant analogue of C1-INH purified from the milk of transgenic rabbits. C1-INH acts by inhibiting kallikrein and suppressing bradykinin formation resulting in increased plasma levels of C1-INH activity. All 3 C1-INH products are intravenously (IV) administered. Nontherapeutic proteins may be found in these products, but the impact of these proteins on safety,

such as immunogenicity and efficacy, is unknown.²⁶ Purity may also play a role in immunogenicity; purity was highest for rhC1-INH (Ruconest) (98.6%), followed by the plasma-derived C1-INH, Berinert (97%) and Cinryze (89.5%).²⁷ Haegarda was not available at the time this comparison was evaluated.

Ecallantide (Kalbitor) is a recombinant selective, reversible inhibitor of the plasma protein kallikrein. When ecallantide binds to kallikrein the conversion of HMS kinogen to bradykinin is blocked. Ecallantide is administered SC.

Icatibant (Firazyr) is a selective synthetic bradykinin B2 receptor antagonist. Icatibant has similar receptor affinity as bradykinin. Icatibant is administered SC.

PHARMACOKINETICS^{28,29,30,31,32,33}

Drug	Cmax	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
ecallantide (Kalbitor)	586 ng/mL	2-3	2	nr	renal
icatibant (Firazyr)	974 ng/mL	0.75	1.4	extensively metabolized by proteolytic enzymes to inactive metabolites	renal
pdC1-INH [Human] (Berinert)	nr	nr	24	nr	nr
pdC1-INH [Human] (Cinryze)	0.68-0.85 units/mL	2.7-3.9	56-62	nr	nr
pdC1-INH [Human] (Haegarda)	60.7 (%) ‡	59	69	nr	nr
rhC1-INH [recombinant] (Ruconest)	1.2-1.3 IU/mL	0.3	2.4-2.7	nr	nr

Cmax = maximum serum concentration; Tmax = time to maximum serum concentration

‡ Cmax: 2.5-97.5 percentile of the population

CONTRAINDICATIONS/WARNINGS^{34,35,36,37,38,39}

C1-INH products (Berinert, Cinryze, Haegarda, Ruconest) are contraindicated in patients with known serious hypersensitivity to the product. Hypersensitivity reactions may include hives, urticaria, tightness of chest, wheezing, and hypotension. If hypersensitivity reaction is suspected, C1-INH should be discontinued and treatment of hypersensitivity reactions should be carefully considered since symptoms are similar to HAE. Epinephrine should be prescribed for patients on C1-INH therapy for immediate use for acute severe hypersensitivity reactions.

Recombinant C1-INH (Ruconest) is also contraindicated in patients with a known allergy to rabbits or rabbit-derived products.

Use of ecallantide (Kalbitor) is contraindicated in patients with a known hypersensitivity to the product. Boxed warnings advise that ecallantide should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE. Patients should be observed for an appropriate period of time after administration of ecallantide.

There are no contraindications reported for icatibant (Firazyr).

Thromboembolic events (TE) have been reported in patients receiving C1-INH. Risk factors for TE include presence of an indwelling venous catheter, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptive or androgen therapy, morbid obesity, and immobility.

Since plasma-derived C1-INH agents (Berinert, Cinryze, Haegarda) are derived from human blood, there is a potential for transmission of infection.

In addition to self-administering acute treatment with C1-INH (Berinert, Haegarda) or icatibant (Firazyr) for an acute HAE attack, patients should be instructed to seek immediate medical attention if laryngeal involvement is present.

The B2 receptor has been associated with cardioprotective effects of bradykinin and antagonism of this receptor has the potential to result in negative cardiovascular effects after acute ischemia. Icatibant (Firazyr) should be used with caution in patients with unstable angina and acute coronary ischemia and during the weeks following a cerebrovascular accident.

DRUG INTERACTIONS^{40,41,42,43,44,45}

No drug interactions studies have been performed with C1-INH (Berinert, Cinryze, Haegarda, Ruconest) or ecallantide (Kalbitor).

Icatibant (Firazyr) has the potential to increase the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors.

ADVERSE EFFECTS^{46,47,48,49,50,51}

Drug	Headache	Nausea	Rash	Vomiting	Abdominal Pain	Pyrexia	Injection Site Reaction	Diarrhea
ecallantide (Kalbitor)	11	13	3	6	5	5	3-7	11
icatibant (Firazyr)	reported	reported	reported	nr	nr	4 (0)	97 (25)	nr
pdC1-INH [Human] (Berinert)	7 (11.9)	7 (26.2)	3.5	2.3 (16.1)	7 (11.9)	nr	reported	0 (19)
pdC1-INH [Human] (Cinryze)	19	18	10	10	nr	5	reported	nr
pdC1-INH [Human] (Haegarda)	nr	nr	reported	nr	nr	nr	28-35 (24)	nr
rhC1-INH [recombinant] (Ruconest)	9	2	reported	nr	≥2	nr	nr	2

Other common adverse reactions reported for ecallantide (Kalbitor) include fatigue (12%), upper respiratory tract infection (8%), and nasopharyngitis (6%). In clinical studies, serious thrombotic adverse events were observed with pdC1-INH (Cinryze) including cerebrovascular accident (< 1%)

The most common adverse reactions that occurred in at least 4% of C1-INH (Haegarda) patients included injection site reactions, hypersensitivities, nasopharyngitis, and dizziness.

Because C1-INH (Berinert, Cinryze, Haegarda, Ruconest), is a therapeutic protein, there is potential for immunogenicity; however, no anti-C1 esterase inhibitor antibodies have been detected. There is no evidence that resistance develops with C1-INH treatment.

Presence of antibodies to ecallantide (Kalbitor) has been reported in approximately 20% of patients treated with ecallantide. Neutralizing antibodies were discovered in 8.8% of patients and did not lead to reduced efficacy. Rates of seroconversion increase with increased exposure to ecallantide and patients who seroconvert may be at increased risk of hypersensitivity reactions.

In clinical studies, anti-icatibant antibodies were detected in 4 patients, of which 3 patients had subsequent negative tests for antibodies. No change in efficacy or incidence of hypersensitivity was observed.

SPECIAL POPULATIONS^{52,53,54,55,56,57}

Pediatrics

The safety and efficacy of pdC1-INH (Cinryze) has not been established in patients < 18 years. The safety profile of C1-INH (Berinert) in the pediatric population was found to be similar to that observed in adults. The safety and effectiveness of C1-INH (Haegarda) was evaluated in a subset of 6 patients aged 12 to < 17 years old. The outcomes of the subgroup were consistent with overall study results. Recombinant C1-INH (Ruconest) is indicated for use in adolescents and studied in patients ≥ 13 years.

Ecallantide (Kalbitor) is approved for use in patients ≥ 12 years of age. Data on the effectiveness of ecallantide in 12 to 15 year old patients, which showed similar drug exposure in adult and adolescent patients, were extrapolated to patients ≥ 16 years of age.

Safety and efficacy of icatibant (Firazyr) have not been established in patients < 18 years of age.

Geriatrics

The number of subjects ≥ 65 years of age were not sufficient in studies of pdC1-INH (Berinert, Cinryze), rhC1-INH (Ruconest), ecallantide (Kalbitor), or icatibant (Firazyr) to establish differing response from younger patients. The safety and efficacy of Haegarda were evaluated in a subgroup of patients aged 65 to 72 years (n=8); results were consistent with the overall study group.

Pregnancy

Recombinant C1-INH (Ruconest) is Pregnancy Category B based on animal studies. Plasma-derived C1-INH (Berinert, Cinryze, Haegarda) is Pregnancy Category C since no animal data are available. There are no prospective clinical data available to assess the use of C1-INH (Haegarda) during pregnancy. However, C1-INH is a normal component of plasma. Ecallantide (Kalbitor) and icatibant (Firazyr) are Pregnancy Category C.

Hepatic Impairment

No dose adjustment of icatibant (Firazyr) is needed in patients with hepatic impairment.

Use of C1-INH (Berinert, Cinryze, Haegarda, Ruconest) in patients with hepatic impairment has not been evaluated.

No pharmacokinetic data are available for use of ecallantide (Kalbitor) in patients with hepatic impairment.

Renal Impairment

No dose adjustment of icatibant (Firazyr) is needed in patients with renal impairment.

Use of C1-INH (Berinert, Cinryze, Haegarda, Ruconest) in patients with renal impairment has not been evaluated.

No pharmacokinetic data are available for use of ecallantide (Kalbitor) in patients with renal impairment.

DOSAGES^{58,59,60,61,62,63}

Drug	Dosage	Availability
ecallantide (Kalbitor)	30 mg SC administered as 10 mg/mL at 3 anatomical sites: abdomen, thigh, upper arm (site rotation not necessary); May repeat dose within a 24 hour period if attack persists HCP-administered	10 mg/mL solution single-use vial (3 per carton)
icatibant (Firazyr)	30 mg SC abdominally over at least 30 seconds; Additional doses may be administered at interval of at least 6 hours if inadequate response or symptoms recur; No > 3 injections should be administered in 24 hours May be self-administered with proper training	30 mg/3 mL prefilled syringe
pdC1-INH (Berinert)	20 IU/kg IV at a rate of 4 mL/min Doses < 20 IU/kg should not be given May be self-administered with proper training A silicone-free syringe should be used for reconstitution and administration of Berinert	Lyophilized powder for reconstitution; 500 IU/10 mL single-use vial
pdC1-INH (Cinryze)	1,000 units IV every 3 to 4 days at a rate of 1 mL/min (10 minutes) If no response to the above routine prophylaxis dosing: doses up to 2,500 units [U] (not exceeding 100 U/kg) every 3 to 4 days may be considered based on individual response May be self-administered with proper training	Lyophilized powder for reconstitution; 500 units/5 mL single-use vial
pdC1-INH (Haegarda)	60 IU/kg via SC injection twice weekly (every 3 to 4 days)	Lyophilized powder for reconstitution; single-use vials containing 2,000 or 3,000 IU
rhC1-INH (Ruconest)	50 IU/kg IV over 5 minutes; May repeat dose if attack symptoms persist; Do not exceed 4,200 IU per dose; Do not exceed 2 doses in a 24 hour period Body weight < 84 kg: 50 IU/kg Body weight ≥ 84 kg: 4,200 IU (2 vials) May be self-administered with proper training	Lyophilized powder for reconstitution; 2,100 IU/25 mL single-use vial

HCP = health care professional; SC = subcutaneously; IU = international units; IV = intravenous

pdC1-INH (Berinert, Cinryze) and rhC1-INH (Ruconest) infusions should not be mixed with other medicinal products and should be administered in a separate infusion line.

pdC1-INH (Haegarda) preservative-free solution should be used within 8 hours of reconstitution

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human

participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in U.S., single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

C1 esterase inhibitors, plasma-derived (Berinert)

IMPACT-1: The safety and efficacy of pdC1-INH were evaluated in a placebo-controlled, double-blind, parallel-group, clinical study that enrolled 124 subjects who were experiencing an acute moderate to severe attack of abdominal or facial HAE.^{64,65} Age range of subjects was from 6 to 72 years. The time to onset of relief of symptoms was assessed based on patient questionnaires of individual symptoms and the severity of each symptom over time. Subjects were randomized into 3 groups to receive a single dose of pdC1-INH of 10 IU/kg or 20 IU/kg of body weight, or a single dose of placebo administered by slow IV infusion within 5 hours of a HAE attack. If sufficient relief of symptoms was not experienced by 4 hours after the infusion, study investigators had the option to give a blinded rescue dose as a second dose of pdC1-INH at 20 IU/kg for the placebo group, 10 IU/kg for the 10 IU/kg group, or placebo for the 20 IU/kg group. All subjects who received rescue medication were regarded as non-responders and the time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (including rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief. Subjects treated with pdC1-INH 20 IU/kg experienced a faster onset of symptom relief as compared to placebo (0.5 versus 1.5 hours, respectively; $p=0.0025$), regardless of the location of the attack (face or abdomen). The difference in the time to onset of relief from symptoms between the pdC1-INH 10 IU/kg group and the placebo group was not statistically significantly different. Within 60 minutes after the administration of study medication, 62.8% of subjects in the pdC1-INH 20 IU/kg group reported onset of symptom relief versus 26.2% in the placebo group. The median time to complete resolution of symptoms was significantly shorter with pdC1-INH 20 IU/kg compared with placebo (4.9 versus 7.8 hours, respectively; $p=0.0237$). Approximately 30% of subjects required rescue medication in the pdC1-INH 20 IU/kg group compared to about 55% in the placebo group.

C1 esterase inhibitors, plasma derived (Cinryze)

A single randomized, double-blind, placebo-controlled multicenter cross-over study evaluated the safety and efficacy of pdC1-INH prophylaxis therapy to reduce the incidence, severity, and duration of HAE attacks.⁶⁶ This study enrolled 24 HAE patients with a history of at least 2 HAE attacks per month. Age range in the study was 9 to 73 years. Patients were randomized to 1 of 2 treatment groups: either pdC1-INH prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis or placebo prophylaxis for 12 weeks followed by 12 weeks of pdC1-INH prophylaxis. Doses were given every 3 to 4 days, approximately 2 times per week. Patients kept a daily record of any new angioedema symptoms that

were not present the previous day. The efficacy determination was based on the comparison of the number of attacks during the 12-week period while receiving pdC1-INH versus placebo. Mean number of attacks was 6.1 for the study drug as compared to 12.7 for placebo ($p<0.0001$). Mean duration of HAE attacks reported was 2.1 days for pdC1-INH and 3.4 days for placebo. The number of days swelling was reported was 10.1 for pdC1-INH and 29.6 for placebo. Mean severity was less with the study drug, 1.3 versus 1.9, based on a 3-point scoring system (1=mild, 2=moderate, 3=severe).

C1 esterase inhibitors, plasma derived (Haegarda)

COMPACT trial:^{67,68} The safety and efficacy of C1-INH, a nanofiltered, plasma derived, C1 inhibitor preparation was established in a phase 3, double-blind, randomized, placebo-controlled, 32-week, cross over study in 90 patients with a diagnosis of type I or type II HAE. Patients with ≥ 4 attacks in a consecutive 2-month period within 3 months before study screening were included. Patients were randomly assigned to 1 of 4 treatment groups, with each involving two 16-week treatment periods. Patients received either 40 IU or 60 IU per kg of C1-INH, which was self-administered SC twice weekly followed by placebo, or vice versa. The primary efficacy endpoint was the number of angioedema attacks. The secondary efficacy endpoint were the proportion of patients who had a response and the number of times a rescue medication was used. A response was defined as a $\geq 50\%$ reduction in the number of attacks while on C1-INH as compared with placebo. Of the 90 patients randomized to groups, 79 completed the study. Both doses of C1-INH, compared to placebo, reduced the incidence of attacks. The 40 IU group experienced 2.4 less attacks per month compared to placebo with a response rate of 76% ($p<0.001$) and the 60 IU group experienced 3.5 lesser attacks per month when compared to placebo ($p<0.001$) with a 90% response rate. Additionally, rescue medication utilization was also reduced compared to placebo. The 40 IU group only required rescue medication of 1.1 uses per month compared to placebo's 5.6 uses per month ($p=0.018$). The 60 IU group only required 0.3 uses of rescue medication compared to placebo's 3.9 uses ($p<0.001$). The severity of attacks in the treatment arms were also less severe. Adverse events were mild and similar across all study groups.

C1 esterase inhibitors, recombinant (Ruconest)⁶⁹

The safety and efficacy of rhC1-INH in the treatment of HAE acute attacks were demonstrated in a placebo-controlled, double-blind, randomized study (Study 1). Supportive evidence of effectiveness is provided by a double-blind, randomized, placebo-controlled study (Study 2).

Study 1: A double-blind, placebo-controlled trial that included an open-label extension evaluated the efficacy and safety of rhC1-INH 50 IU/kg in the treatment of acute HAE attacks in adults and adolescents (age range of 17 to 69 years).⁷⁰ Patients were randomized to receive rhC1-INH 50 IU/kg ($n=44$) or placebo ($n=31$). The primary efficacy endpoint was the time to onset of symptom relief as documented by patient-reported questionnaires. Primary efficacy was assessed by patient responses on a Treatment Effect Questionnaire (TEQ). Rescue medication was allowed for patients who had no symptom improvement at 4 hours after study drug administration, or earlier if life-threatening oropharyngeal-laryngeal angioedema symptoms occurred. If a patient required rescue medication prior to achieving initial relief of symptoms, the time to initial relief of symptoms was recorded as the last time the TEQ was assessed prior to medication use. In the blinded phase, the median time to onset of symptom relief was statistically significantly shorter in patients treated with rhC1-INH compared to those treated with placebo (90 versus 152 minutes, respectively; $p=0.031$). Median time to minimal symptoms was 303 minutes in rhC1-INH group compared to 483 minutes in the placebo group

($p=0.078$). A lesser proportion of patients in the rhC1-INH group received rescue medication compared to the placebo group (11% versus 42%, respectively). Among patients who achieved relief within 4 hours, 27% ($n=4$) of patients in the placebo group had a relapse of their symptoms within 24 hours versus 3% ($n=1$) for the rhC1-INH group.

Data from planned subgroup analyses in U.S. patients showed that the median time to onset of symptom relief with persistence was 98 minutes for those receiving rhC1-INH ($n=22$) and 90 minutes for those receiving placebo ($n=16$). Median time to onset of symptom relief for non-U.S. patients receiving rhC1-INH ($n=22$) was 90 minutes and 334 minutes for those receiving placebo ($n=15$). In addition, analysis of gender subgroups suggested a greater treatment response in men than women. The median time to onset of symptom relief was 113 minutes for women receiving rhC1-INH ($n=28$) compared to women receiving placebo of 105 minutes ($n=19$). In men, these values were 75 minutes ($n=16$) and 480 minutes ($n=12$), respectively. No explanations for the regional or gender subgroup responses were found; however, it was noted that there was a larger-than-expected placebo response among U.S. women.

In Study 2 (North American controlled trial), patients ranging in age from 17 to 66 years were randomized to receive a single dose of either rhC1-INH 50 IU/kg ($n=12$), rhC1-INH 100 IU/kg ($n=13$), or placebo ($n=13$). The efficacy of rhC1-INH in the treatment of acute HAE attacks was demonstrated by significantly shorter time to onset of symptom relief based on the Visual Analogue Assessment Scores (VAS). A VAS decrease of at least 20 mm as compared to baseline with persistence of improvement at 2 consecutive time points was deemed as onset of symptom relief.

ecallantide (Kalbitor)⁷¹

EDEMA-3: The safety and efficacy of ecallantide were assessed in a randomized, double-blind, placebo-controlled trial of 72 patients with HAE assigned to receive ecallantide or placebo for acute attacks. The primary efficacy endpoint was measured with the Treatment Outcome Score (TOS), a measure of symptom response at 4 hours after dose administration; a value > 0 reflected an improvement in symptoms from baseline. The key secondary efficacy endpoint was the change from baseline in Mean Symptom Complex Severity (MSCS) at 4 hours after the dose was administered. Patients treated with ecallantide experienced a significantly greater TOS than patients treated with placebo (63 versus 36, respectively; $p=0.045$) and a significantly greater decrease from baseline in the MSCS than placebo (-1.1 versus -0.6 , respectively; $p=0.041$). In addition, 36% of patients in the placebo group required medical intervention to treat unresolved symptoms within 24 hours compared to 14% in the ecallantide group.

EDEMA-4: The safety and efficacy of ecallantide were assessed in a randomized, double-blind, placebo-controlled trial of 96 HAE patients assigned to receive ecallantide 30 mg SC or placebo for acute attacks of HAE. The primary endpoint was the change from baseline in MSCS score at 4 hours, and the key secondary endpoint was TOS at 4 hours. Patients treated with ecallantide experienced a significantly greater decrease from baseline in the MSCS than placebo (-0.8 versus -0.4 , respectively; $p=0.01$) and a significantly greater TOS than patients with placebo (53 versus 8, respectively; $p=0.003$). At 24 hours, patients treated with ecallantide also reported a greater decrease from baseline in the MSCS than placebo (-1.5 versus -1.1 , respectively; $p=0.04$) and a greater TOS (89 versus 55, respectively; $p=0.03$).

icatibant (Firazyr)

FAST-1 & 2:⁷² The efficacy and safety of icatibant 30 mg SC injection was evaluated in 2 phase 3 randomized, double-blind, controlled clinical trials in patients with HAE who presented within 6 hours of an acute attack with cutaneous or abdominal symptoms. In FAST-1, 56 patients received either icatibant or placebo; in FAST-2, 74 patients received icatibant or oral tranexamic acid 3 g once daily for 2 consecutive days. The primary efficacy endpoint in both trials was the median time to clinically significant relief of the index symptom, which was defined as the symptom (cutaneous swelling, cutaneous pain, or abdominal pain) with the highest score on the VAS measured prior to study drug administration. Abdominal pain was the index symptom for patients experiencing a combination of all 3 symptoms. In FAST-1, the time to clinically significant relief was not statistically significant between the icatibant group and placebo group (2.5 versus 4.6 hours, respectively; $p=0.14$). Although, as assessed by the patient and the investigator, the median time to first symptom improvement was significantly shorter in the icatibant group compared with the placebo group (0.8 hour versus 16.9 hours, respectively; $p<0.001$; and 1 hour versus 5.7 hours, respectively; $p<0.001$). In the FAST-1 study, 3 patients in the icatibant group and 13 in the placebo group needed rescue medication. In FAST-2, primary endpoint was reached in 2 hours for icatibant and 12 hours for tranexamic acid; the difference was statistically significant ($p<0.001$). No icatibant-related serious adverse events were reported.

FAST 3:⁷³ In a randomized, placebo-controlled, double-blind, parallel-group study of 98 adults with HAE, patients received either a single dose of icatibant 30 mg or placebo by SC injection, given within 6 hours of onset of HAE symptoms. Patients with severe laryngeal attacks of HAE received open-label icatibant 30 mg. The primary endpoint was assessed with a VAS that included average assessments of skin swelling, skin pain, and abdominal pain. The median time to a response, defined as at least a 50% reduction from the pretreatment composite 3-item VAS score, for patients with cutaneous or abdominal attacks treated with icatibant, was 2 hours compared to 19.8 hours for placebo-treated patients ($p<0.001$). In addition, the median time to almost complete symptom relief was 8 hours for icatibant and 36 hours for placebo. Seven percent of patients in the icatibant group received rescue medication versus 40% in the placebo group.

SUMMARY

Hereditary angioedema (HAE) is a rare genetic disorder that results in low levels of endogenous or functional C1 esterase inhibitor (C1-INH). HAE is characterized by recurrent episodes of SC or submucosal edema involving the skin or mucosal tissues of the upper respiratory and GI tracts. Accurate diagnosis of HAE due to C1INH deficiency is critical for proper treatment.

Plasma-derived concentrates of human plasma-derived C1-INH (Berinert, Cinryze) and a recombinant analogue of C1-INH (Ruconest) are available as IV injections; while, human plasma-derived C1-INH (Haegarda) is available as a SC injection. Ecallantide (Kalbitor) is a selective inhibitor of the plasma protein, kallikrein, and is administered SC. Icatibant (Firazyr) is a selective synthetic bradykinin B2 receptor antagonist and is also administered SC. All agents, with the exception of ecallantide, may be self-administered with proper training. Cinryze is FDA-approved for prophylactic use, while the remaining agents are indicated for treatment of HAE attacks. Thromboembolic events (TE) have been reported in patients receiving C1-INH. Although pasteurized and purified, since C1-INH agents (Berinert, Cinryze, Haegarda) are derived from human blood, there is a small potential for transmission of infection. Recombinant C1-INH (Ruconest) does not have this precaution. Icatibant (Firazyr) should

be used with caution in patients with unstable angina and acute coronary ischemia and in the weeks following a stroke, due to the potential for negative cardiovascular effects. Headache and nausea are common adverse effects reported. Injection site reactions are most commonly reported with use of icatibant (Firazyr).

While all agents have established effectiveness in clinical trials, no head-to-head studies have been performed for the agents in the review. Per current clinical guidelines, C1-INH (Berinert, Cinryze, Ruconest), ecallantide (Kalbitor), and icatibant (Firazyr) are all considered first line therapy for the treatment of HAE attacks; one agent is not preferred over another; Haegarda was not available at the time of the current guideline development. Furthermore, it should be noted that whereas, the C1-INH agents and ecallantide may treat adolescents and adults, plasma-derived C1-INH (Berinert) is currently FDA-approved to treat both adults and all ages within the pediatric population.

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